

disease or death rates large enough to be of concern to us should become manifest. Ideally, subjects should be offered different contraceptive methods in accordance with a randomized allocation scheme. In some circumstances the random allocation procedure may be impractical and one must try to achieve relative comparability of groups in other ways. There are likely to be other difficulties as well—losses from observation, refusal to continue with periodic examinations, and the like—but none of these difficulties is insuperable and none, in my opinion, justifies the very nearly complete absence of such studies in this field.

In fact, one of the earliest studies initiated on oral contraceptives was a controlled prospective study. After initial exploration, starting in 1960, established the very nearly complete effectiveness of the pill, Dr. Gregory Pincus and others initiated such a study in Puerto Rico in 1962. Although sound in design, the study was beset with a number of administrative difficulties and, after the death of Dr. Pincus, it has come to be regarded in some quarters as a lost cause. The study is nonetheless still on-going and it represents the only long-term prospective controlled study of the pill in existence. Early reports from this study were highly favorable to the pill, but these reports also have been subjected to unfavorable criticism and the study is not at present accepted as a substantial contribution to our knowledge on the problem of safety.

Regarding thromboembolic disease. Early case reports led to the suspicion that the use of oral contraceptives might be leading to an increase of thromboembolic disease, and the pill has correspondingly been considered as contra-indicated in cases of circulatory disorder. However, until quite recently no important studies of this problem were carried out in this country. Last year two British studies were reported (Inman and Vessey; Vessey and Doll) and, at the request of the FDA advisory committee, a similar study was carried out in this country under the supervision of Professor Philip Sartwell of the Johns Hopkins University. In addition, vital statistics related to thromboembolic disease were reviewed.

The British studies have been hailed as models of clinical study design and appear to have been taken in most quarters as incontrovertible evidence of a pill-induced increase of thromboembolic disease. The Sartwell report, similar in design and at least equal in thoroughness and care in execution, indicates an increased risk of hospitalizable, nonfatal thromboembolic disease. Let me interpolate that it was an interview study post-hospitalization, and therefore, of necessity was concerned only with nonfatal diseases. This conclusion is widely accepted and perhaps prudence requires us at least to take it as a working hypothesis, and to evaluate the seriousness of the implied increased risk. (The risk of excess mortality due to thromboembolic disease is estimated from other studies to amount to approximately three deaths per 100,000 per year.) However, for the reasons indicated in my letter to Dr. Ortiz—see attached—I find this type of evidence to be far from convincing. Suspicions about oral contraceptives and thromboembolism have long been current and could readily have led to somewhat different hospitalization rates for women suffering similar disorders according to whether or not